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Original Research

Treatment sequence with either irinotecan/cetuximab followed by FOLFOX-4 or the reverse strategy in metastatic colorectal cancer patients progressing after first-line FOLFIRI/bevacizumab: An Italian Group for the Study of Gastrointestinal Cancer phase III, randomised trial comparing two sequences of therapy in colorectal metastatic patients

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KEYWORDS
Metastatic colorectal cancer;
Treatment strategy;
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Treatment sequence

Abstract ***Introduction:*** The optimal treatment strategy for RAS wild type (WT) mCRC is controversial. Our phase III study investigated the effect of introducing earlier (second-line) or later (third-line) cetuximab in patients progressed after FOLFIRI/bevacizumab first-line.
Patients and methods: mCRC patients progressing after FOLFIRI/bevacizumab first-line were randomised to receive second-line irinotecan/cetuximab followed by third-line FOLFOX-4 (arm A) or the reverse sequence (arm B). Primary end-point was progression-free survival (PFS).
Results: About 54 and 56 patients were randomised in arm A and in arm B, respectively. After a median follow-up of 37.5 months, 100 PFS events were recorded. Median PFS was 9.9 months in arm A and 11.3 months in arm B (Hazard ratio [HR] 1.04, 95% confidence interval [CI]: 0.69–1.56, p = 0.854), while median overall survival was 12.3 months in arm A and 18.6 months in arm B (HR 0.84, 95% CI: 0.55–1.28; p = 0.411). No overall difference in side-effects were observed between the two treatment arms.
Conclusions: This trial did not meet the primary end-point (PFS). Like other preclinical and clinical evidences, our study seems to suggest a reduced activity of cetuximab after a first-line bevacizumab-based therapy.

1. Introduction

Colon cancer is the second most common malignant disease in developed countries [1]. The introduction of treatment options such as oxaliplatin and irinotecan combinations, and more recently agents directed against the epidermal growth factor receptor (EGFR, cetuximab and panitumumab) or tumour-driven angiogenesis (bevacizumab, aflibercept and ramucirumab) determined an impressive improvement in median overall survival (OS) from the initial 6 months to the current 30 months. Concomitantly, the extensive use of effective predictive markers also represented a new successful opportunity in order to select the best treatment for each patient. The translation into clinical practice of the use of K-RAS first and K-RAS and N-RAS then for EGFR-targeted agents opened, in fact, the way to a true personalised approach [2].

In spite of these encouraging results, several controversial issues remain unanswered. In particular, the definition of the best up-front combination as well as the optimal treatment sequence is still a matter of debate, especially in RAS wild-type tumours.

The present trial, initially designed in 2008, aimed to verify different clinical assumptions about the optimal first-line treatment and the global therapeutic strategy for metastatic colorectal cancer patients. Although we knew that either first-line FOLFOX or FOLFIRI were equally active, findings from the GERCOR study suggested that FOLFOX second-line might determine a better response rate (RR) and progression-free survival (PFS) in this setting [3]. Furthermore, at the time when the present study was designed first-line bevacizumab-based therapy preferentially included irinotecan. Based on these considerations we then decided to investigate the use of FOLFOX second-line in metastatic colorectal cancer patients progressing after first-line irinotecan-based chemotherapy.

Further considerations in the specific subset of RAS wild type (WT) colorectal tumours might suggest that cetuximab in combination with chemotherapy represented a preferable choice over bevacizumab [4]. Nonetheless cross comparisons of clinical data also indicated that on the one hand the clinical activity of bevacizumab faded across subsequent treatment lines, while on the other hand cetuximab retained a comparable clinical activity throughout all lines [5–7]. These findings implied that cetuximab was in fact the only effective treatment available for third-line therapy within a possible treatment strategy, particularly, when neither regorafenib nor TAS-102 was available [8,9].

Taking all these assumptions into account we designed a phase III randomised trial to compare the efficacy and safety of two different treatment sequences: second-line irinotecan/cetuximab followed by third-line FOLFOX-4 versus second-line FOLFOX-4 followed by third-line irinotecan/cetuximab in K-RAS WT patients progressing after first-line FOLFIRI/bevacizumab.

Although both these treatment strategies were considered a standard of care approach in 2008, findings from the FIRE-3, CALGB and PEAK trials [10–12] recently indicated that EGFR inhibitors in combination with chemotherapy might now be the preferred first-line choice in RAS WT tumours. Moreover, second-line treatment with EGFR-directed monoclonal antibodies may be currently questioned in view of the bevacizumab beyond progression strategy as suggested by the TML and BEBYP trials [13,14].